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Pitfalls in spirometry: Clinical relevance

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Abstract

Spirometry is one of the functional tests most used in respiratory medicine to assess lung function in health and disease conditions. Its success is grounded on solid principles of lung mechanics that state that maximal flow on expiration is limited by the physical properties of airways and lung parenchyma. In contrast, on inspiration, flow depends on the force generated by the inspiratory muscles. Reduced expiratory forced flow and volumes usually reflect a deviation from health conditions. Yet due to a complex interplay of different obstructive and restrictive lung diseases within the multiple structural dimensions of the respiratory system, flows and volumes do not always perfectly reflect the impact of the disease on lung function. The present review is intended to shed light on a series of artefacts and biological phenomena that may confound the clinical interpretation of the main spirometric measurements. Among them is thoracic gas compression volume, the volume and time history of the inspiratory manoeuvre that precedes the forced expiration, the effects of heterogeneous distribution of the disease across the respiratory system, and the changes in lung elastic recoil.

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Key words: Spirometry; Thoracic gas compression vol-

ume; Volume history effects of the deep breath; Time history effects of the preceding inspiratory manoeuvre; Ventilation heterogeneities; Lung elastic recoil; Clinical interpretation

Core tip: Spirometry is usually taken as a marker of the disease and its progression independently of the condition. In the present review we partly challenge this notion by examining the role of different obstructive and restrictive lung diseases on a series of mechanisms that strongly affect the main spirometric parameters. Among them is thoracic gas compression volume, the volume and time history of the inspiratory manoeuvre that precedes the forced expiration, the effects of heterogeneous distribution of the disease across the respiratory system, and the changes in lung elastic recoil.

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INTRODUCTION

Current knowledge of the mechanisms determining forced expiratory flows and volumes in respiratory diseases is still incomplete. According to the principles of lung mechanics, maximum ventilation is achieved by activating the respiratory muscles to overcome resistive, elastic and inertial forces of the respiratory system^[1-3]. During a forced inspiratory manoeuvre flow reaches a peak at about 50% of vital capacity (VC) because this is the volume at which the difference between the pleural pressure generated by the force of the inspiratory muscles^[1] and the elastic, resistive and inertial pressures is maximal. Reducing inspiratory effort causes a parallel decrease in flow, which suggests that maximum inspiratory flow is limited by the force of the inspiratory muscles. Narrowing of extra- or intra-thoracic central airways may also

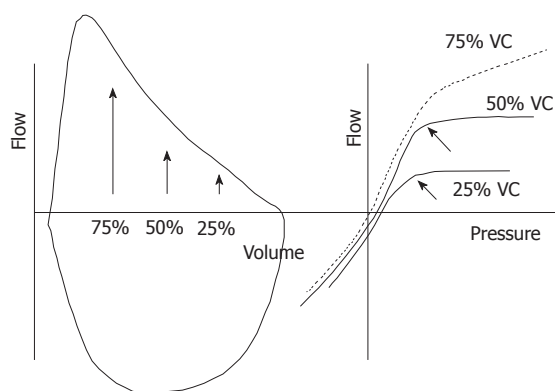


Figure 1 Relationship between maximum flow, volume and pleural pressure. Left panel: Flow-volume curves during inspiratory and expiratory manoeuvres. The arrows indicate the volume at 75%, 50%, and 25% vital capacity; Right panel: flow and pleural pressure (Ppl) relationships during expiratory manoeuvres at different lung volumes. At 25% and 50% vital capacity (VC) flow plateaus at different pressures (oblique arrows). In contrast, at 75% VC flow keeps increasing with the increase of pressure. The lack of increased expiratory flow at 25% and 50% VC despite the increase in Ppl supports the concept of expiratory flow limitation.

contribute to limiting inspiratory flow. During a forced expiration, flow depends on the mechanical properties of airways and lung over most of VC rather than the expiratory effort. A peak expiratory flow (PEF) is on average achieved in less than 120 ms after the start of the expiratory effort. Thereafter, flow decreases almost linearly with lung volume. That expiratory flow is limited during forced expiration can be demonstrated by plotting flow *vs* transpulmonary pressure at iso-volume: flow increases monotonically with pressure at high lung volume but then reaches a plateau at mid-to-low lung volumes (Figure 1). Several theories have been proposed to explain the phenomenon of expiratory flow limitation (EFL).

The equal pressure-point theory^[4] predicts that during forced expiration, the driving force for flow, *i.e.*, alveolar pressure (Palv), decreases with decreasing lung volume to a point at which it equals pleural pressure (Ppl). This is called the equal pressure point (EPP). Under these conditions, the airways tend to collapse. Downstream from this segment, the airways will oscillate between different physical configurations depending on the fluctuation of intrabronchial relative to extrabronchial pressure. When this condition is achieved, flow becomes maximal and cannot increase no matter how the expiratory effort is increased or pressure at the mouth is lowered. The EPP first develops within the intrathoracic trachea and then shifts to the sublobar or segmental bronchi with the decrease in Palv. This model allows partitioning the airways located upstream from the EPP where flow is determined by Pel and upstream resistance, thus reflecting most of the structural changes occurring with lung diseases, and those lying downstream from the EPP where flow is controlled by central airways resistance.

Permutt *et al*^[5] interpreted the EFL on the basis of a Starling resistor. In brief, with the gradual decrease of Palv when gas moves from the alveoli to the mouth, there

will be a time when Palv decreases and reaches a critical value similar to Ppl. The collapsible segment will then narrow and self adjust in size in a way that inlet pressure equals Ppl and outlet pressure is determined by flow and resistance of the downstream segment.

More recently, the EFL phenomenon has been interpreted on the ground of the pressure-area (P-A) relationship and Bernoulli effect^[1]. The concept here is that choke points (CP) form during a forced expiration depending on elastic properties of the airways and pressure loss necessary to accelerate gas from a large surface (alveoli) to central airways. As a result, the higher the airway size and stiffness of the airway wall at the CP the higher maximum flow and vice versa.

Recognition that maximum expiratory flow depends on the physical properties of the lung and airways upstream from the CP represents the most solid rationale for using spirometry in clinical practice and research to assess and locate the structural changes caused by respiratory diseases. Noninvasiveness of the technique, easiness to perform the manoeuvre, low cost of instrument, and standardization of the technique with reference equations explain the widespread use of spirometry around the world^[6].

If all this fully supports the use of spirometry in respiratory medicine, the last two decades however, have brought to light a series of artefacts that may confound the interpretation of the spirometric signals and data in different respiratory diseases.

THORACIC GAS COMPRESSION VOLUME

During a forced expiration, the effort causes an increase in Palv that exceeds the pressure necessary to generate maximal flow^[7,8]. This is a function of absolute lung volume and airflow resistance. As a result, part of the thoracic gas is compressed and the forced expiratory volume in 1 s measured at the mouth by spirometry (FEV₁) is therefore less than that simultaneously measured from the changes in a body plethysmograph (FEV_{1-PL}) which is void of the effects of thoracic gas compression (Figure 2, upper panel). This phenomenon results in a negative effort-dependence of FEV₁ and is clinically relevant for interpretation of lung function in disease as well as the changes occurring with medical interventions on airways or lung volume^[9]. On average, in healthy subjects the difference between FEV_{1-PL} and FEV₁ is about 4%^[10]. However, in obstructive lung diseases this may reach values up to 100%^[11,12], depending on airflow resistance and amount of intrathoracic gas. A typical example is shown in Figure 2, lower panel. This phenomenon is clinically relevant for interpretation of lung function in disease and with medical interventions on airways or lung volume. Unpublished data from our Lab show that for a given airflow resistance, the FEV₁ in Chronic obstructive pulmonary disease (COPD) is significantly higher in the patients with predominant bronchiolitis than emphysema. This is because in emphysema absolute lung

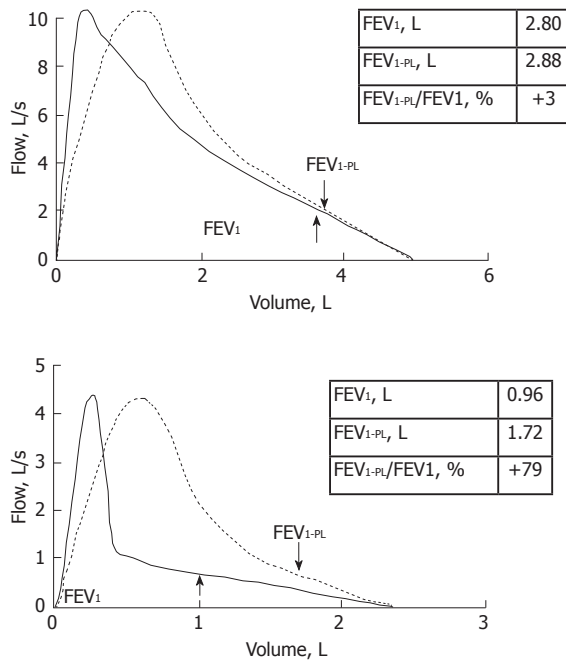


Figure 2 Effects of thoracic gas compression volume on spirometry. Flow at the mouth is plotted against volume integrated from the flow signal (continuous line) or measured in a volume-compensated body plethysmograph (dashed line). The FEV₁ at the mouth (FEV₁) and in the plethysmograph (FEV_{1-PL}) are indicated. The volume difference between the loops is the volume compressed within the chest wall during the forced expiratory manoeuvre (TGCV) and that does not contribute to the exhaled gas. Upper panel refers to a normal subject. The difference between FEV_{1-PL} and FEV₁ is 3%. Lower panel refers to a patient affected by chronic obstructive pulmonary disease with prevalent emphysema. TGCV is very large because of lung hyperinflation in addition to airflow obstruction. FEV_{1-PL} is 79% greater than FEV₁.

volume is higher than in chronic bronchitis. It follows that grading the disease on the FEV₁ as suggested by current international guidelines may lead to overestimate the severity of airflow obstruction in emphysema compared to chronic bronchitis and, as a result, overload the patients with inappropriate kind and amount of medications. In a recent study, Sharafkhaneh *et al*^[11] reported that inhaling a bronchodilator agent was associated with a significant decrease in thoracic gas compression volume during forced but not tidal expiratory manoeuvres. This was due to a decrease in lung resistance and dynamic hyperinflation, and accounted for 23% of the increase in FEV₁, thus seriously confounding the interpretation of the dilator response based on the FEV₁. In other words, the FEV₁ significantly overestimated the number of positive bronchodilator responses. In another study, the same group showed that 40% of the increase in the FEV₁ after lung volume reduction surgery was explained by the decrease in thoracic gas compression volume (TGCV)^[12]. Very recently, we examined the relationship between bronchial responsiveness or reversibility tests using FEV₁ and height and sex, which are major determinants of lung volume^[9]. Airway responsiveness to methacholine was assessed in 54 asthmatics; bronchodilator response to salbutamol was assessed in 55 subjects with reversible airflow obstruction. The methacholine provocative dose

was significantly greater using FEV_{1-PL} than FEV₁, with this difference being significantly correlated with alveolar pressure, total lung capacity and height, and larger in males than females. Of the 55 subjects who responded to salbutamol with an increase of FEV₁ > 200 mL and > 12% of control, 28 did not show an increase of FEV_{1-PL} above these thresholds. These subjects were significantly taller, predominantly males, with larger total lung capacity (TLC) and greater alveolar pressure than their counterpart. Thus, it appears that the bronchoconstrictor and bronchodilator responses are overestimated by standard spirometry in subjects with larger lungs because of the large TGCV.

Taken together, these findings strongly suggest that any changes in lung volume and/or airflow resistance no matter how they are achieved significantly confound the interpretation of the classical spirometric parameters.

VOLUME HISTORY EFFECTS OF THE DEEP BREATH

A second major factor that importantly affects spirometry is the full breath taken prior to full expiration. This was first described in 1961 by Nadel *et al*^[13] in healthy subjects exposed to a constrictor agent. Taking a deep breath reversed the increase in airway resistance^[13]. Subsequent studies proved that forced expiratory flow was higher during a maximal than a partial manoeuvre started from lower lung volume, and this increased with the severity of airway narrowing^[14,15]. This effect on flow was also associated with a decrease in residual volume, suggesting that volume history modulates not only airway narrowing but also closure^[16]. Studies conducted in asthmatics exposed to a provocative agent documented an increase in maximal compared to partial flow, thus suggesting bronchodilation. Yet this was remarkably less than in healthy subjects. During natural asthma attacks indeed, the deep breath did not relieve bronchospasm or caused even more narrowing^[17]. Similar responses were reported in COPD^[18]. Reducing bronchial tone with a β_2 -adrenoceptor agonist prevented maximal flow from increasing as much as partial flow, suggesting some modulation of airway tone by deep breath^[19]. Reducing airway inflammation in asthma with inhaled steroids restored the bronchodilator effect of deep breath^[20]. Thus, depending on the kind and severity of disease and medical interventions, the spirometric indexes are affected by the deep breath preceding the forced expiratory manoeuvre. Typical examples are shown in Figure 3.

In few asthmatic patients, taking one or more deep breaths may cause airway narrowing as suggested by important decrements of FEV₁^[21]. This phenomenon was attenuated by a voltage-dependent Ca²⁺-channel blocker, thus suggesting a myogenic response triggered by stretching airway smooth muscle cells.

These findings fuelled interest on the mechanisms causing airway narrowing. Based on the relative hysteresis hypothesis of Froeb *et al*^[22], the airways dilate on inspi-

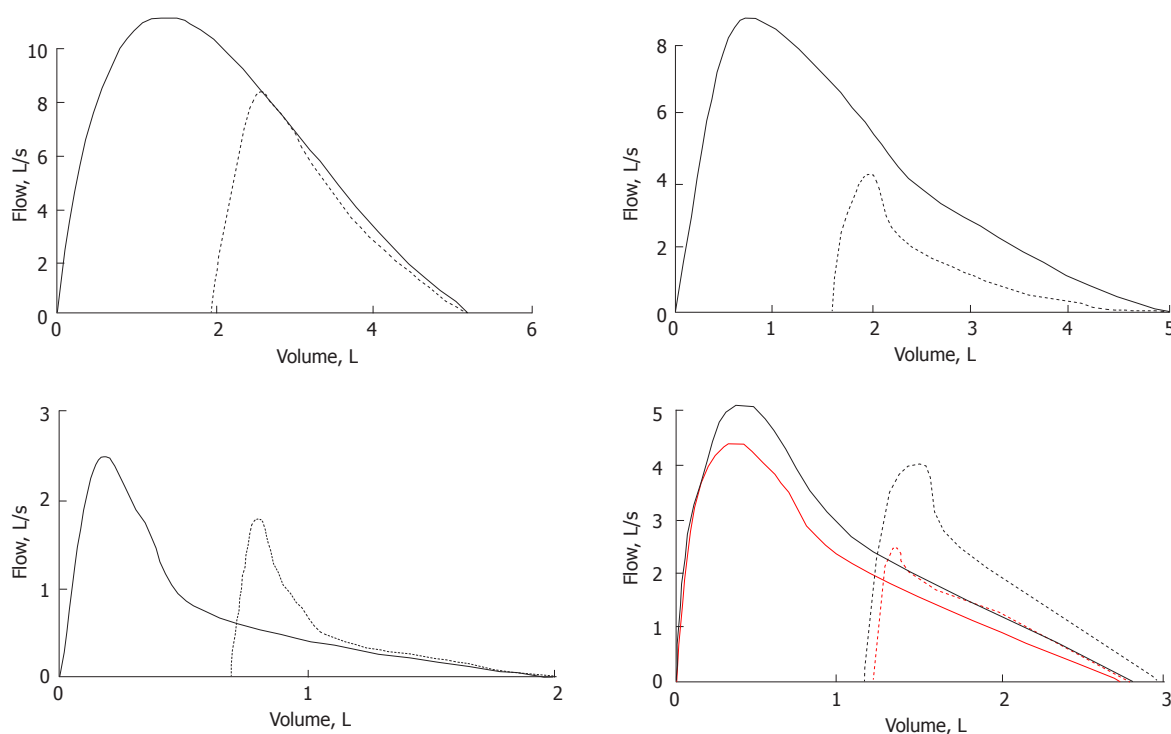


Figure 3 Examples of the effects of the deep breath on maximum flow and volume depending on the disease condition. Continuous and dashed lines are maximal and partial flow-volume loops, respectively. Upper left panel is a normal case. The slight increase in flow after DB suggests a decrease of normal bronchial tone presumably provided by the vagus nerve. Upper right panel is the case of a mild asthmatic subjects during a bronchial challenge. The increase in flow after the deep breath indicates that a substantial part of the constrictor response to the chemical agent is ablated with DB. Lower left panel is the case of a patient affected by chronic obstructive lung disease in which taking a DB is associated with a decrease of flow. This is presumably due to the involvement of the peripheral lung regions that contribute to the lung elastic recoil and/or loss of airway-to-parenchyma interdependence. Lower right lung is the case of an asthmatic subject before and after (red and black lines, respectively) inhaling a bronchodilator agent. Isovolumetric flow measured during manoeuvres initiated from mid lung volumes (dashed lines) is higher than flow after a maximum lung inflation (continuous lines).

ration as a result of the increase in lung elastic recoil. However, because both airways and lung parenchyma are imperfect elastic materials, part of the energy stored on inspiration is dissipated on expiration. If this is the same for airways and lung parenchyma, then airway calibre and thus flow at a given lung volume will be the same on inspiration and expiration. If in contrast, it is the airways that mostly dissipate energy during cycling rather than lung parenchyma, then airway calibre will be larger on expiration than inspiration and the opposite will happen if pressure dissipates more within lung tissue than airways. This theory would suggest that the bronchodilator effect of the deep breath during induced bronchoconstriction might be the result of a decrease in airway smooth muscle tone when stretched by a large breath. Conversely, reducing airway smooth muscle tone by inhaling bronchodilators would reduce airway smooth muscle pressure dissipation, thus causing maximal flow to be less than partial flow. Similarly, an increase in airway wall stiffness due to chronic remodelling processes would prevent the airways from distending with large breaths. Finally, loss of pressure within lung parenchyma would result in a reduction of maximal below partial flow, though the underlying mechanisms at tissue or cellular level are unknown.

Altogether, these findings point out to the disease condition and severity as crucial modifiers of bronchial tone after a deep breath and thus classical spirometric indexes.

TIME HISTORY EFFECTS OF THE PRECEDING INSPIRATORY MANOEUVRE

Duration of the full inspiration preceding the forced expiratory manoeuvre also plays some role on the major spirometric indexes in different conditions such as health^[23,24], airflow obstruction^[24,25], cystic fibrosis^[26], and interstitial lung disease^[27]. In brief, under all these conditions, increasing the duration of the inspiratory manoeuvre and end-inspiratory pause is associated with a decrease in PEF and FEV₁ that is about 20%-30% compared with fast manoeuvres with no pause at maximal lung inflation. Loss of lung elastic recoil with the slow inspiratory manoeuvres has been suggested as the mechanism underlying the decrease in flow, though recruitment rate of closed or near closure airways might also play a role. The time history of the forced expiratory manoeuvres assumes clinical relevance mostly when inspiration is severely slowed down as a result of inspiratory muscles fatigue or severity of airway narrowing.

VENTILATION HETEROGENEITIES

Normal lungs exhibit structural and functional heteroge-

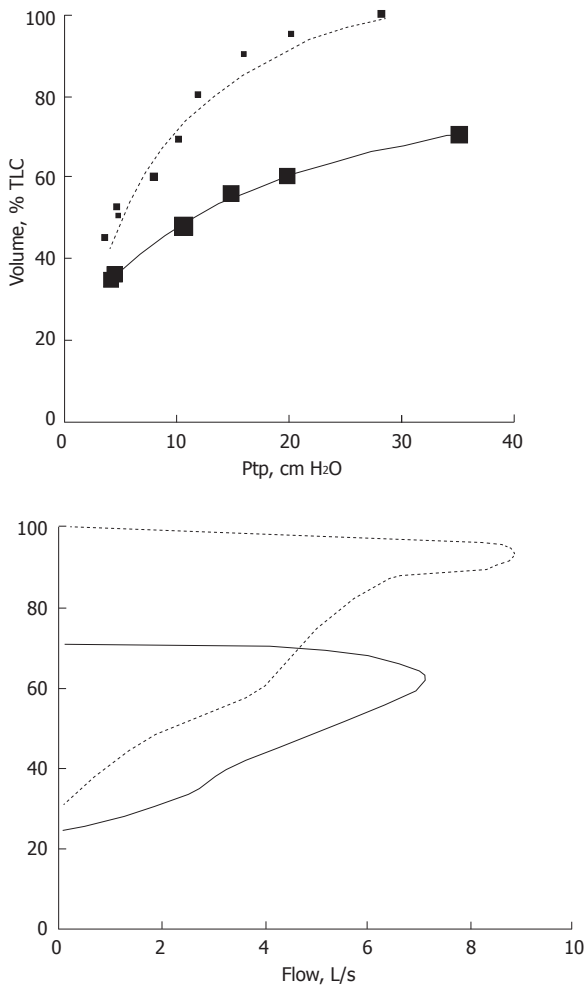


Figure 4 Effects of increased lung elastic recoil on maximal flow in a healthy subject (dashed lines) and a patients affected by pulmonary fibrosis (continuous lines). Upper panel: transpulmonary pressure (Ptp) is plotted vs lung volume; Lower panel: flow is plotted vs volume. With the increase in Ptp, maximal flow increases. This compensates for the decrease in FEV₁ expected from the decrease in total lung capacity (TLC).

neities^[28-30] that contribute to modifying maximal flows and volumes.

For instance, central airways obstruction causes a decrease in maximum flow at high lung volume and a shift of the choke point to low lung volume^[31]. This is because airway calibre, wall compliance, or both are reduced. Vital capacity is not reduced under these conditions because small airways are not affected by the disorder. In contrast, increasing peripheral airway resistance will cause flow to decrease over the entire range of lung volume, and choke point to shift to higher lung volume. This is because frictional and/or convective pressure losses are increased with a resulting decrease in transmural pressure and airway area at choke point. Forced vital capacity is reduced, because small airways tend to close at increased lung volume.

Also parallel ventilation inhomogeneities tend to reduce forced expiratory flow, but this effect appears to be less important compared to the above discussed in series heterogeneities. The idea is that they may be somewhat counterbalanced by compensatory mechanisms. This was

investigated by Solway *et al.*^[32] with the use of an electrical analogue. By introducing different types of parallel inhomogeneities, the Authors produced multiple axial choke points. Surprisingly however, flow-volume loops exhibited near normal configurations. The interpretation was that lung regions with higher driving pressure emptied faster, thus contributing to maintaining overall ventilation near normal. Wilson *et al.*^[33] examined flow at the junction of two tubes emptying with different driving pressures upstream from the flow-limiting segment. Flow from the region with higher driving pressure was higher than flow from the region with lower driving pressure, thus suggesting a sort of mechanical compensatory mechanism keeping ventilation near normal during forced emptying. McNamara *et al.*^[34] measured alveolar pressure in excised dog lungs with the help of alveolar capsules. Despite appreciable pressure differences between regions, expiratory flow-volume loops were normal or near normal. All this provides evidence of different kinds of flow interdependence between and within lobes that mask the effect of parallel heterogeneity on lung emptying.

In conclusion, serial heterogeneities appear to affect the main spirometric parameters more than parallel heterogeneities. This might help explain why in the early stages of obstructive or restrictive lung diseases that are characterized by heterogeneous ventilation, spirometry is still normal or near normal despite the presence of initial structural damage.

LUNG ELASTIC RECOIL

Lung elastic recoil is one of the major determinants of maximum flow as anticipated in the introductory section of this review. If in emphysema the decrease in Pel is reflected by a decrease in FEV₁, the increase in Pel in interstitial lung diseases is not associated with an increase in FEV₁. This is because of a reduction in lung volume. However, examining maximum flow as a function of absolute lung volume will show that for any given lung volume, flow is higher than predicted value because of the increase in Pel^[35] (Figure 4). In patients with combined emphysema and pulmonary fibrosis^[36] the decrease in flow and thus FEV₁ due to emphysema is usually well compensated by the increase in lung recoil due to pulmonary fibrosis. As a result, the FEV₁ is still normal. Under these conditions, TLC will also be normal because the loss of alveolar units due to pulmonary fibrosis is compensated by the increased enlarged emphysematous airspaces.

DYSANAPTIC LUNG GROWTH

In childhood, the airways and lung parenchyma usually grow proportionally so that in adulthood the FEV₁ will be about 80% of VC. In a small number of healthy young adults however, the FEV₁ is normal, but the ratio of FEV₁ to VC is surprisingly below normal range. In a recent study^[37], it was reported that about 20% of these

cases had a history free of any respiratory symptoms or diseases and no abnormalities could be detected even with additional pulmonary function tests. The pattern is consistent with asynchronous development of airways and air spaces during the early stages of life^[38], with some individuals having lung parenchyma disproportionately growing faster and to a greater extent than airways. Among the hypothetical mechanisms, natural events such as intense physical activity or disease conditions occurring before definite maturation of the respiratory system have been reported. Under these conditions, it is suggested that the subjects undergo further functional evaluation to exclude a disease condition.

CONCLUSION

Spirometry is one of the most used tests in medicine and research because of its good sensitivity to detect pulmonary function defects, easiness and noninvasiveness of the manoeuvre, standardisation of the technique, and low cost of the instruments. Yet, it must be acknowledged that many factors significantly contribute to amplify or blunt its changes in disease conditions. As the FEV₁ and VC are the classical parameters used by current guidelines for the diagnosis of pulmonary defects and severity grading, spirometry should always be included within a panel of functional tests capable of thoroughly examining lung function within its whole volume and time domains.

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Update on diagnosis and treatment of pulmonary alveolar microlithiasis

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Abstract

Pulmonary alveolar microlithiasis (PAM) (MIM265100) is a rare disease characterized by the diffuse deposit of microlithiasis in alveolar spaces. PAM could occur worldwide with high prevalence in Asia and Europe. Familial occurrence indicates its autosomal recessive trait and the *SLC34A2* gene was identified as the responsible gene for the disease. In spite of the versatile mutation sites in patients from other countries, exon 7 and exon 8 might be the most liable gene in Chinese and Japanese patients. Most mutations caused the premature termination of proteins and produced truncated proteins, leading to the blocking of the recycling and degrading of outdated surfactant which is full of phospholipids. The most outstanding clinical feature of PAM is the discrepancy between the paucity of symptoms and the degree of pulmonary involvement. Diagnosis is easy to establish based on typical chest radiograph image and nuclear medicine improves its early diagnosis and active evaluation. Pathology of the unique intra-

alveolar lamellar microliths gives strong support for diagnosis. No effective treatment is considered valid currently. However, lung transplantation is effective for advanced-stage patients, and long term treatment of disodium etidronate seems promising.

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Key words: Pulmonary alveolar microlithiasis; *SLC34A2*; Mutation; Chest computed tomography; Treatment

Core tip: Pulmonary alveolar microlithiasis (PAM) is a rare disease and lack of enough acknowledgements. The present review provides a comprehensive description on the latest progress in the genotype and treatment of PAM. *SLC34A2* is identified as the responsible gene and its mutation in patients from different countries has showed versatile symbols, whilst Chinese and Japanese patients only involved exon 7 and exon 8. The diagnosis of PAM could be established on typical chest radiograph image. Though currently no effective regimens are valid to cure the diseases, long term treatment of disodium etidronate seems promising.

Wang HY, Zhou NY, Yang XY. Update on diagnosis and treatment of pulmonary alveolar microlithiasis. *World J Respirol* 2014; 4(3): 26-30 Available from: URL: <http://www.wjgnet.com/2218-6255/full/v4/i3/26.htm> DOI: <http://dx.doi.org/10.5320/wjr.v4.i3.26>

INTRODUCTION

Pulmonary alveolar microlithiasis (PAM) (MIM265100) is a rare disease characterized by the diffuse deposit of microlithiasis in alveolar spaces^[1]. Ever since its first description by Malpighi in 1686 and nomination by Pühr^[2] in 1933, cases of PAM have been reported all over the world successively, including several reviews with large

size of cases^[3-5]. Those reports play an important role in the acknowledgement of epidemiological, pathological, radiological and clinical feature of PAM. However, those reviews usually only collected cases written in English for analysis, and many cases such as Chinese patients that written in local language were unfortunately ignored. Thus the recognition of PAM is unavoidably biased. Moreover, the recent identification of the responsible gene, *SLC34A2*, and update of long term follow-up sheds new light on its genetic etiology and therapy. The present review summarizes the recent findings of the disease mainly focusing on genetic etiology, clinical diagnostic methods and therapy regimen, together with the data from Chinese patients of PAM, aiming to provides more comprehensive view of PAM.

UPDATE ON EPIDEMIOLOGY

PAM occurs worldwide. According to Mariotta's report in year 2004, in which 576 cases in international literature from 51 countries were reviewed, Europe was the most prevalent continent and Turkey had the highest number of PAM patients^[3]. Whereas the prevalence in Asia was severely underestimated for many cases published in local journals were unavailable for analyzing. For example, Tachibana *et al*^[4] reported 105 cases in Japan by year 2001, while only 32 cases were obtained in international literature. The same condition happened in Chinese data, even more severe. Recently, we searched Chinese cases of PAM and obtained 200 cases since the first cases reported in 1965. Combined with Tachibana's data, it seems the prevalence of PAM in Asia is actually significantly higher than Europe and China is also one of the countries predominated with PAM. Yet, no evidence demonstrates regional clustering of patients in China either.

Average familial occurrence is about one third of 576 cases^[3]. Whilst, the ratio is significantly higher in those countries with high number of cases, such as Japan (50% of 111 cases)^[6], Turkey (48% of 52 cases)^[1], Italy (43.7% of 48 cases)^[5] and China (56% of 200 cases). The feature that those familial patients are horizontal siblings from inbred families strongly indicates its autosomal recessive trait. However, even putting into the consideration of the low rate of family screen, there still are large parts of sporadic patients.

The age at diagnosis of PAM varied from neonatal to eighties. But most patients are found at the second or third decade. Japanese patients are the youngest group with 52.3% under 15^[6], the mean age of patients in other countries are at twenties. And Chinese patients showed 10-year delay of age at diagnosis, which is probably due to the low international healthcare and routine checkup. Sex difference was not seen at prevalence, diagnosis age and progression in most areas, except for China and Turkey where male patients had high prevalence^[1].

UPDATE ON GENETIC AND MECHANISM

Though PAM has been postulated as an autosomal recessive

disease, it was until year 2006 that Corut *et al*^[7] first identified a PAM locus to chromosome 4p15 by homozygosity mapping, and suggested that the *SLC34A2* gene cause PAM through the genotyping and linkage analysis study on a larger Turkey family. Meanwhile, Huqun *et al*^[8] employed a modified homozygosity mapping method and discovered homozygous exonic mutations on exon 8. They further confirmed this conclusion through the function assay of mutant protein *in vitro*. Therefore, the *SLC34A2* gene was identified as the responsible gene for PAM. And the following articles described versatile mutation symbols of the *SLC34A2* gene in 14 PAM cases mainly from Turkey, China and Japan, as we analyzed previously^[9-17]. These mutations demonstrated point deletion^[7,14], pointed mutation^[7,9,14-16], deletion plus insertion mutation^[8], small fragment deletion and target fragment deletion^[11]. Most of these mutations involved the exons and homozygous mutation is the common character of these studies. However, a significant phenomenon needs to be noted is that the mutations in Turkish patients happened on several exons, whilst only exon 7 and exon 8 are affected in Chinese and Japanese patients. Especially in China, two positive reports of studies that performed genotyping in PAM patients, both found homozygous mutations on exon 8^[12,13,15]. Moreover, we recently found a compound heterozygous mutation from a sporadic Chinese patient also showed an involvement of exon 8^[18]. Therefore, we hypothesize that exon 8 might be the most vulnerable site in Chinese patients, surely more case studies or experiments are needed to confirm it.

Despite the versatile symbols most mutations caused the premature termination of proteins and produced truncated proteins through either affecting the protein produce or abolishing gene expression. *SLC34A2* is a type II b sodium phosphate co-transporter primarily expressing in alveolar type II cells, and the only known sodium-dependent phosphate transporter expressed in the lung^[19]. This protein plays the role of clearing the phospholipids from the alveolar space through transporting the phosphorus ion into the alveolar type II cells. The mutated proteins lose their function and lead to the blocking of the recycling and degrading of outdated surfactant which full of phospholipids, which finally results in the formation of microliths.

However, the molecular structure-function relationship of this protein is still poorly understood. While back to previous reports of PAM, only Huqun *et al*^[8] performed the function study of the expressed protein through the assay of phosphate uptake by *Xenopus* oocytes, which was microinjected with transcribed *in vitro* wild-type RNA or mutant RNA of *SLC34A2*. Even though, it only confirmed the association of *SLC34A2* in this disease, but didn't demonstrate the relative function region of the protein or the mutant. In our recent investigation, we took the advantage of bioinformatic technology and predicted the 3-D structure using online software, demonstrated the main functional domain of wild type NaPi-IIb and the possible transportation sites through the summary of changes in different mutants^[18].

Though the 3-D structure prediction exists unavoidable errors, it still could be a good tool for the investigation of the molecular-function relationship of this protein.

It was speculated whether genotype-phenotype correlation exists in PAM patients. The evidence for that seems lack from the existed reports despite the full penetrance of genetic defect. On the contrary, exogenous factors seem play an important role in the progression in this disease of early onset and very slow development. Heavy smokers seem to have severe phenotype. Infection also accelerates the progression. Recently, de Laurentiis *et al.*^[20] studied the pulmonary cell immune phenotype and concluded that CD8⁺ has the prevalence in the bronchoalveolar lavage fluid (BALF) of PAM patients.

UPDATE ON CLINICAL FEATURE

The most outstanding clinical feature of PAM is the discrepancy between the paucity of symptoms and the degree of pulmonary involvement. The patients of PAM are usually free of symptoms when discovered fortuitously for other diseases or by mass radiograph examination. The disease progresses very slowly, even to 30 years, to appear exertional dyspnea or cough^[21]. Lung function keeps normal or slight impaired ventilatory function or diffusing capacity. Whereas, at the advanced stage of the disease, the severe deposits of microstones impaired the gas exchange function of alveolar space and resulted in respiratory insufficiency.

Diagnosis is easy to establish based on the typical chest radiograph. Chest X-ray usually showed bilateral fine sand-like micro-nodulation of calcific densities throughout both lung fields mainly involved the middle and lower zone, sometimes producing a “sand-storm” appearance. On high resolution computed tomography (HRCT) it presented the wildly diffused microliths deposit in air-space, which caused consolidation of the affected area. High density calcification of this consolidated area, mediastinal window, and pleura together with interlobular septa shaped as a contour. This unique manifestation of radiograph makes it a strong method in detecting of PAM patients, for most of those patients are not aware of their disease without clue of symptoms. The magnetic resonance of imaging with the hypointensity or a signal void on T1- and T2-weighted images of the calcification lesions provides little value in PAM, while the development of nuclear medicine gives more help on the contrary. The absorption of Tc-99m labeled diphosphonate compounds, which have a natural affinity for calcification foci at the soft-tissue level, help to detect early pulmonary calcification^[22]. And the uptake of ¹⁸F-fluoro-deoxyglucose on combined positron emission tomography/computed tomography may be useful to evaluate the pulmonary inflammation or predict the prognosis of the patients of PAM^[23,24].

Microliths in sputum or BALF under bronchoscope examination then give strong support for diagnosis. Pathology of lung biopsy and autopsy specimens are im-

portant for proved diagnosis but not necessary. It demonstrates the unique intraalveolar lamellar microliths, which is highly correlated with CT findings^[25]. Chemical analysis revealed that these microstones consist of calcium and phosphates. Nevertheless, genotyping assay of *SLC34A2* could further clinch the diagnosis.

Blood tests including serum calcium and phosphate concentration and different steroids are unremarkable, since only the imbalance of calcium and phosphate only happened in microenvironment of alveolar space. Serum surfactant proteins A and D were discovered remarkable elevation in parallel with the deterioration of the lung function^[26]. Therefore, they were suggested as the candidate marker for monitoring the activity of the disease.

Comorbid or extrapulmonary calcification is not common. Though there are some reports of associated milk alkali syndrome, mitral stenosis, pericardiac cyst, *etc.*^[27-29]. The study of the mutation in *SLC34A2* also explained some extrapulmonary calcification such as testicular microlithiasis^[7], or the development of aortic valve calcification and arteriosclerosis^[30].

UPDATE ON LONG-TERM THERAPY REGIMEN

No effective treatment is considered valid currently. Though developing slowly, one of our patients even achieving spontaneous remission^[31], the long-term prognosis of the disease is poor. Most patients died of respiratory failure resulting from the chronic interstitial inflammation and fibrosis finally. The removal of microlithiasis *via* repeated bronchoalveolar lavage without improvement in radiography was not as effective as it in pulmonary alveolar proteinosis^[32].

Lung transplantation has been thought the only expecting regimen especially for patients with severe respiratory failure and right heart failure. The transplantation has demonstrated good effects on the regression of right heart failure^[33]. However, most transplantation is bilateral to avoid the persistent shunting of blood, which also limited its application. The reported data is very limited and lack of the long term follow up. The longest follow up duration is 15 years after lung transplantation^[34]. Thus, the timing for surgery and the possibility of recurrence in the future are still needed to be considered.

Disodium etidronate, a diphosphonate, has been used to treat PAM for many years. Göcmen *et al.*^[35] first introduced it to treat patients of PAM for its role of inhibiting the formation of new pulmonary calcium-phosphate crystallization and resolving previously formed calcifications, and gained clinical improvement and radiological stabilization. The following clinical trials with little or no benefit questioned this regimen^[36,37]. However, Ozcelik *et al.*^[10] recently published their new reports describing the beneficial effects of long-term treatment (9 and 11 years of treatment, respectively) with disodium etidronate in two cases with PAM diagnosed in childhood. They considered that the factors such as the onset of initial treat-

ment, duration and the dosage of the medicine could influence the result of the treatment.

However, in most of Chinese patient who always attacked by acute infection, active treatment of antibiotics and bronchial dilator results in quick improvement and prevention for further deterioration.

CONCLUSION

PAM is a rare genetic disease with autosomal recessive trait occurring worldwide. The *SLC34A2* gene was considered as the responsible gene and exon 8 was the most liable mutation sites in Chinese patients. The mutation usually caused the premature termination of protein and produced truncated protein to induce the accumulation of microliths in alveolar space. The most outstanding clinical feature of PAM is the discrepancy between the paucity of symptoms and the degree of pulmonary involvement. Diagnosis is easy to establish based on the typical chest radiograph. But the nuclear medicine improves its early diagnosis and active evaluation. No effective treatment is considered valid currently. However, lung transplantation is effective for advanced-stage patients, and long term treatment of disodium etidronate seems promising.

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- 2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

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Statistical data

Write as mean \pm SD or mean \pm SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom

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Italics

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